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TECHNOLOGY

Intravascular ultrasound imaging of angiographically normal coronary arteries: a prospective study in vivo

Junbo Ge, Raimund Erbel, Thomas Gerber, Günter Görge, Lothar Koch, Michael Haude, Jürgen Meyer

Abstract

Intravascular ultrasound imaging (IVUS) was performed to elucidate the discrepancy between clinical history and angiographic findings and to measure the diameter and area of the lumen of the normal left coronary artery in 55 patients who presented with chest pain but had normal coronary angiograms. The left coronary artery (LCA) was scanned with a 4·8F, 20 MHz mechanically rotated ultrasound catheter at 413 sites. Atherosclerotic lesions were identified at 72 (17%) sites in 25 patients. The mean (SD) (range) plaque area was 5·55 (3·56) mm² (2–26 mm²) and it occupied 28·8 (9·6)% (13–70%) of the coronary cross sectional area. Calcification was detected at 24 (33%) atherosclerotic sites in nine patients. The correlation coefficients for the lumen dimensions measured at normal sites by IVUS and by angiography were r = 0·93 (SEE = 0·43) mm for lumen diameter and r = 0·89 (SEE = 4·27) mm² for lumen area (both p < 0·001). 16 of the 30 patients in whom no atherosclerotic plaques were detected in the LCA lumen by IVUS had no risk factors of coronary artery disease. The cross sectional area of 90 consecutive images of left main coronary artery (LMCA), proximal left anterior descending coronary artery (proximal LAD), and mid LAD was measured in these 16 subjects. The mean (SEM) areas at end diastole were LMCA 17·33 (7·98) mm²; proximal LAD 13·56 (5·85) mm²; mid LAD 9·75 (4·67) mm². During the cardiac cycle the cross sectional area changed by 10·2 (4·0)% in the LMCA, by 8·3 (4·7)% in the proximal LAD, and by 9·8 (4·0)% in the mid LAD. In 11 patients with plaques the change in cross sectional area in plaque segments (5·8(3·1)%) was significantly lower than in the segments from patients without plaques (p < 0·001). Lumen area reached a maximum in early diastole rather than in late diastole.

IVUS can image atherosclerotic lesions that are angiographically silent; it also provides detailed information about plaque characteristics. The variation in coronary cross sectional area during the cardiac cycle should not be ignored during quantitative analysis. Maximum dimensions in normal segments are reached in early diastole. Further studies are needed to clarify the clinical significance of atherosclerosis detected by IVUS in patients presenting with chest pain but normal coronary angiography.

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Department of Cardiology, University of Essen, Germany
J Ge
R Erbel
G Görge
M Haude

II Medical Clinic, University of Mainz, Germany
T Gerber
L Koch
J Meyer

Correspondence to:
Dr J Ge, Department of Cardiology, University of Essen Hufelandstrasse 55, 4300 Essen, Germany.

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Cardiologists have relied on contract coronary angiography to evaluate vascular morphology and architecture in patients with coronary heart disease. But angiography can only define the contour of the vessel lumen and major structural alterations or abnormalities of the vessels.[1–3] Even with biplane imaging, angiography gives little information on arterial wall thickness and the three dimensional configuration of the vessel lumen. Furthermore, discrepancies between cineangiographic and postmortem findings are considerable, showing that complex and eccentric coronary atherosclerotic lesions are often not identified by angiography.[4 5]

There has been considerable interest in intravascular ultrasound imaging (IVUS), a catheter-based ultrasound technique, because it offers in vivo information on vascular anatomy, physiology, and pathology that has not been available until now.[6–10] Preliminary in vitro and in vivo studies showed that IVUS was a safe, feasible, and accurate method for evaluating vascular morphology.[11–14] Correlations for assessing vessel wall thickness, lumen area, lumen diameter, and perimeter in vitro were excellent,[11–14] but results in vivo remain controversial.[9–11 15]

The purposes of this study were: to compare IVUS with coronary angiography in the evaluation of the morphology of the left coronary artery (LCA); to assess the accuracy and feasibility of IVUS for measuring the dimensions of angiographically normal coronary arteries; to determine the dimensions of the normal LCA; and to study changes in the dimensions of the normal LCA during the cardiac cycle.

Patients and methods

PATIENTS

We studied 55 consecutive patients (28 men

and 27 women aged (mean (SD)) 42–70 years (55·9 (7·2)) who underwent diagnostic coronary angiography for suspected ischaemic heart disease and were found to have angiographically normal coronary arteries. Each gave their informed consent to intracoronary ultrasound imaging. After coronary angiography each patient was given 3000 IU of intracoronary heparin. An 8F or a 9F guiding catheter was used to position the ultrasound catheter for IVUS imaging. A 0·014 inch guidewire was placed in the left anterior descending coronary artery (LAD) and we advanced the imaging catheter over the wire using a monorail technique to obtain coaxial images. The IVUS catheter was then drawn back slowly while the images were recorded in real time and stop frames (every 3–5 mm). The position of the IVUS probe was recorded on an *x* ray film at the points at which the stop frame IVUS images were taken.

INTRAVASCULAR ULTRASOUND DEVICE

We used an IVUS catheter with a 4·8F catheter sheath and a 20 MHz ultrasound transducer inside the catheter (Sonicath, Boston Scientific Corporation, Watertown, MA, USA). The transducer was mechanically rotated within the catheter at 900 rpm to provide cross sectional images on a 512 × 512 pixel ultrasound diagnostic imaging console (Diasonics, Milpitas, CA, USA). A simultaneous electrocardiogram was recorded below the IVUS images. The axial resolution of the catheter is about 150 μm and the lateral resolution is about 300 μm. The images were recorded on half inch S-VHS videotape for off-line analysis.

IVUS IMAGE ANALYSIS

All the IVUS images were digitised (32 frames in series) into a 512 × 512-pixel matrix by an image processing computer (ECHO-COM, PPG Hellige, Freiburg, Germany). The images were stored on a one gigabyte erasable optical disk (Maxtor, The Netherlands). These images were reviewed to identify the best frame, which was magnified by the built-in zoom function to measure the lumen diameter and cross sectional area.

Sixteen of the patients we examined, were regarded as truly normal subjects (see results). Ninety consecutive IVUS images of the LMCA, of the proximal LAD, and of the mid LAD were digitised onto a 256 × 256 pixel format. A semi-automatic software program based on PV-wave (Precision Visuals, Boulder, CO, USA) was developed for the evaluation of the luminal area. Digitised images were evaluated on a SUN SPARC-2 workstation (Mountain View, CA, USA). The program shifted frames to compensate for catheter movement caused by cardiac motion. A region of interest including both the lumen and the vessel wall was defined interactively. Both the vessel wall and lumen were segmented by thresholding. After segmentation the contours of the lumen were superimposed on the original images. If there was a mismatch, for example, caused by signal dropout, we repeated the procedure after correcting the threshold or region of interest. The area of the segmented lumen was measured after the removal of the catheter and guidewire artefact. We displayed the pulsatile variation of the cross sectional area of the lumen over at least three cardiac cycles. For each cardiac cycle we measured the maximum area, minimum area, and ECG-triggered end diastolic area. The IVUS images of the plaque segment in 11 patients were suitable for analysis of the cross sectional area. These values were compared with those of the normal segments in 16 controls.

ANGIOGRAPHIC MEASUREMENT

The cineangiogram was projected onto a 20 × 28 cm screen by an angiogram projection system (CAB-35B, Weinberger, Zürich, Switzerland). The LAD was magnified and drawn. The positions at which the IVUS images had been taken were then superimposed on the drawing. The diameter of the contrast free guiding catheter (8F = 2·67 mm, 9F = 3 mm) was used for calibration; the diameter of the vessel was measured by an image processing computer (Kontron, Cardio-500, Germany). The luminal area was calculated as:

$$A = 1/4.\pi.D^2$$

where A is lumen area and D is lumen diameter.

STATISTICAL ANALYSIS

The values of lumen dimensions were presented as mean (1 SD). We used linear regression and correlation coefficients to examine the relation between the lumen dimensions measured on the IVUS images and those measured by angiography. We also calculated inter and intra observer variation for 30 IVUS images. We used the Paired *t* test to evaluate the variation in the cross sectional area during the cardiac cycle.

Results

MORPHOLOGICAL OBSERVATIONS

We examined 413 sites in 55 patients. IVUS images of normal coronary segment showed a circular or eliptical lumen with a smooth surface (fig 1). We identified atherosclerotic plaques at 72 (17%) sites in 25 (45%) patients. The plaque area was 5·55 (3·56)mm^2 (2–26 mm^2), and it occupied 28·8 (9·6)% (13–70%) of the coronary cross sectional area. Calcification was detected at 24 (33%) sites in nine patients, (fig 2). Most of the plaques (84%) were eccentric (fig 3). None of the patients had obvious stenoses on the coronary angiograms but in one patient with typical angina and a positive exercise ECG, pressure at the catheter tip dropped when it was placed in the left main coronary ostium. There were no obvious abnormalities on angiograms in any projection. IVUS was performed immediately after the angiography in examination during which ischaemic ECG changes occurred. IVUS showed a large

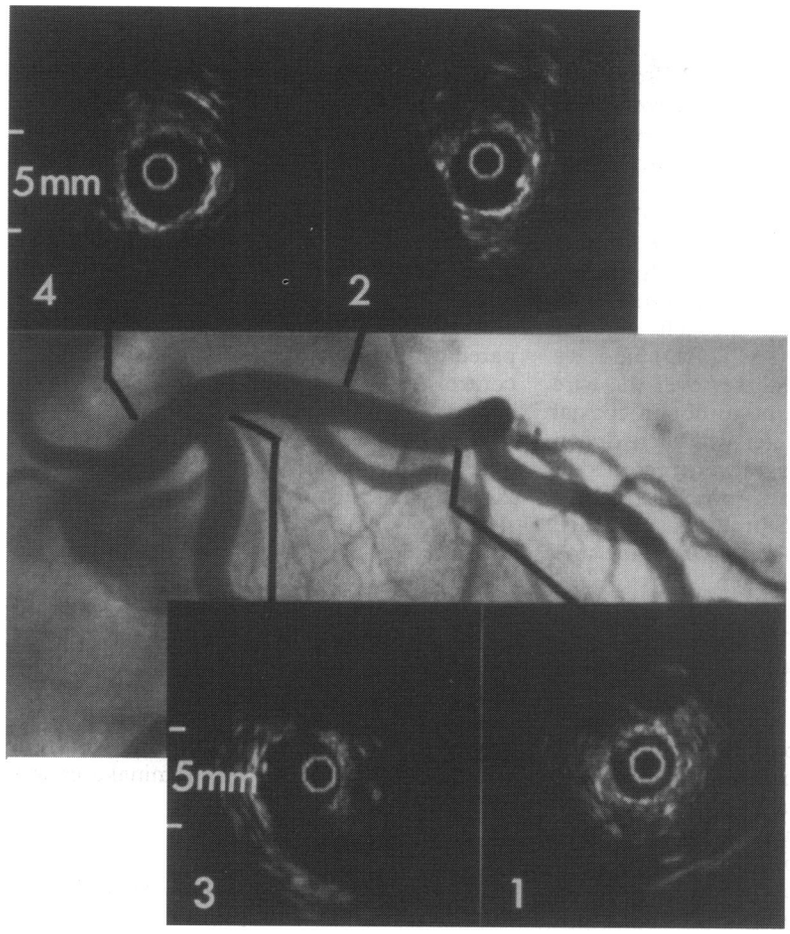

Figure 1 Angiogram and IVUS images at corresponding sites of LCA. No abnormalities were shown by either angiography or IVUS.

plaque in the ostium of the left main coronary artery (fig 4). This finding and the abnormal exercise ECG prompted bypass surgery in this patient.

CORRELATION BETWEEN DIMENSIONS MEASURED BY ANGIOGRAPHY AND BY IVUS

For lumen diameter the intraobserver correlation for 30 IVUS images was $r = 0{\cdot}99$ (SEE 0·16 mm) and the interobserver correlation was $r = 0{\cdot}99$ (SEE 0·17 mm). For lumen cross sectional area the intraobserver correlation was $r = 0{\cdot}99$ (SEE 1·39 mm^2) and interobserver correlation was $r = 0{\cdot}98$ (SEE 1·81 mm^2).

The lumen diameter measured at 341 normalities was 2·7—7·6 mm by IVUS and 2·6–7·3 mm by angiography. Linear regression of the lumen dimensions measured at 100 randomly selected sites showed a close correlation between IVUS and angiography for both lumen diameter and area (fig 5A and B).

NORMAL VALUES OF THE LEFT CORONARY ARTERY

Sixteen (8 men and 8 women, aged 42–68 (mean (SD) 53·6(7·4)) of the 30 patients in whom no plaques in the LCA were detected by IVUS and who had no risk factors for coronary artery disease including systemic hypertension, cigarette smoking, hypercholesterolaemia, and diabetes mellitus were deemed to be truly normal subjects after their negative IVUS examination. Table 1 lists the clinical characteristics of the patients. The cross sectional area of the lumen in group I, who were regarded as normal subjects, was measured frame-by-frame for three to five cardiac cycles. The mean (SD) cross sectional areas of LMCA, proximal LAD, and mid LAD at end diastole (at the beginning of QRS complex) were 17·33 (7·98) mm^2

Table 1 Clinical characteristics of the study population

Characteristic	*Group I (n = 16)*	*Group II (n = 14)*	*Group III (n = 25)*
Age (yrs) (mean (SD))	53·6 (7·4)	55·9 (8·0)	58·8 (6·6)
Men/women	8/8	4/10	16/9
Positive rest ECG	2/16	12/14	17/25
Positive stress ECG	7/16	9/13	12/19
Positive thallum test	6/11	2/4	9/11

Group I = No plaques detected by IVUS and no risk factors for coronary artery disease. Group II = No plaques detected by IVUS; patients had risk factors for coronary artery disease. Group III = Plaques detected by IVUS.

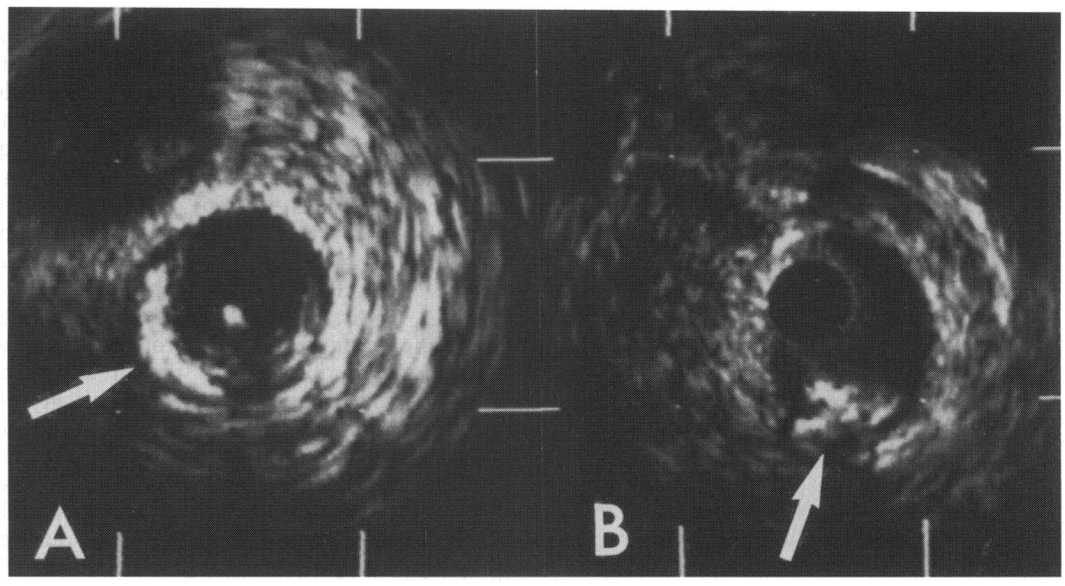

Figure 2 IVUS images of eccentric plaques showing calcified deposits as bright echoes with acoustic shadowing (arrows).

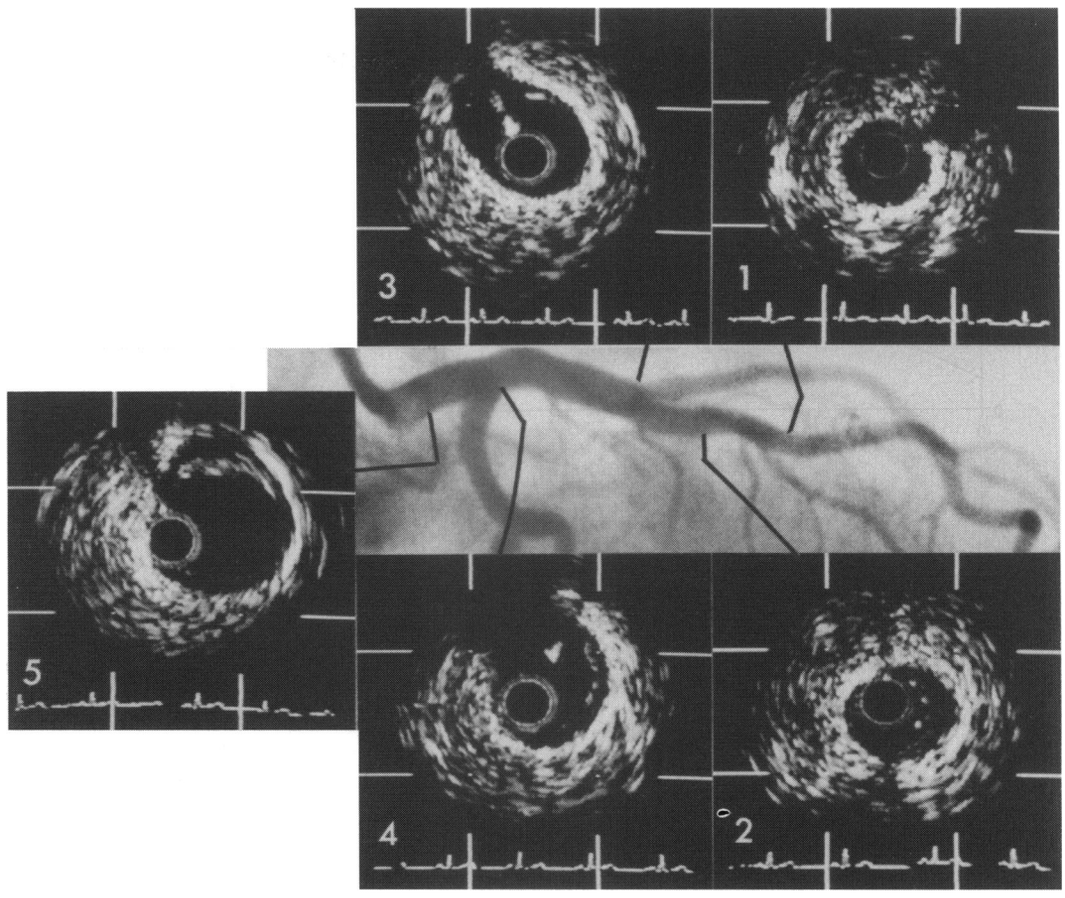

Figure 3 Comparison of an angiogram, showing no abnormality, and IVUS images showing eccentric plaques in the LMCA (position 5) and mid LAD (position 2) in one patient.

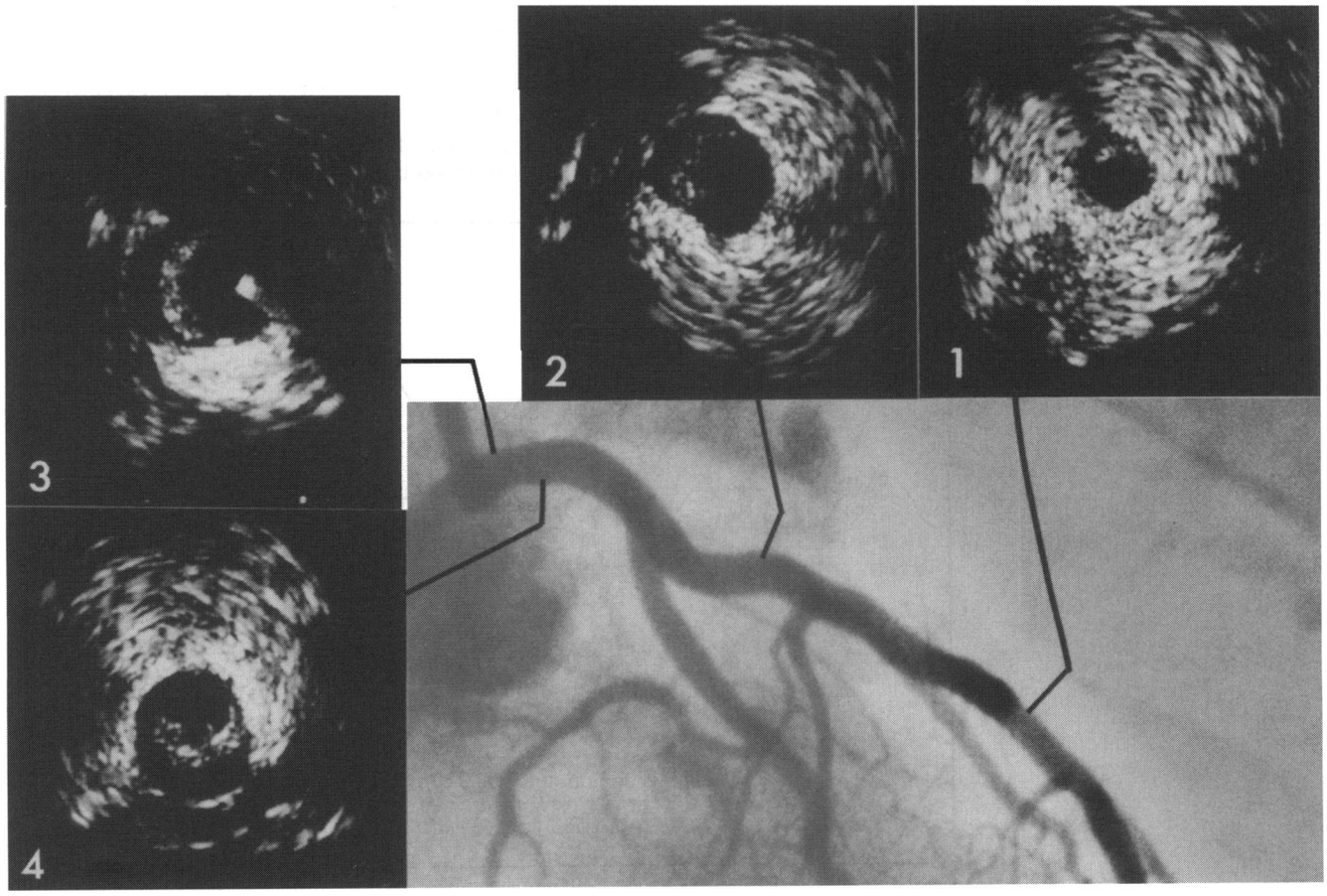

Figure 4 In this 50 year old patient the angiogram was normal but IVUS showed a large eccentric plaque in the ostium (position 3 and 4).

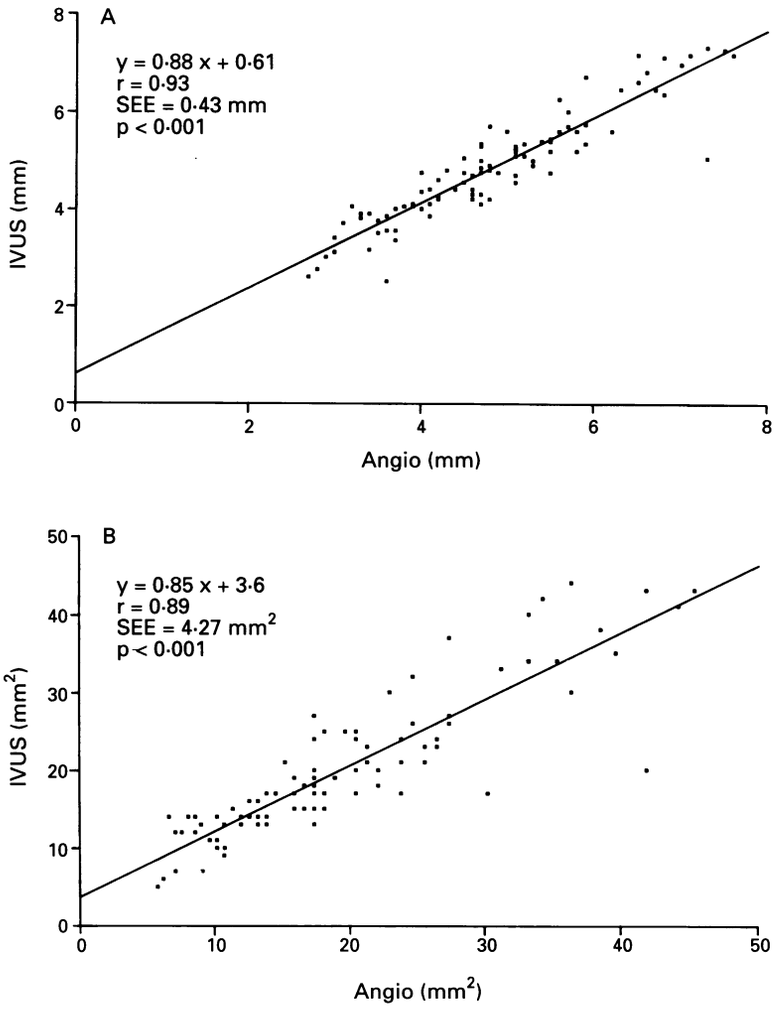

Figure 5 Relation between angiographic (Angio) and ultrasonic measurements (IVUS) of lumen dimensions at normal sites. (A) Lumen diameter; (B) lumen area.

(range 9·12–30·71), 13·56 (5·85)mm² (range 6·42–20·05), and 9·75 (4·67)mm² (range 4·53–22·01). The maximum areas and the end diastolic areas were significantly different (table 2).

PUSATILE VARIATION IN THE CROSS SECTIONAL AREA OF THE LUMEN

The pulsatile variations during the cardiac cycle of the normal patients were 10·2 (4·0)% in LMCA, 8·3(4·7)% in the proximal LAD, and 9·8 (4·0)% in mid LAD. Figure 6 shows the changes in cross sectional area on 90 consecutive frames of 3 to 5 cardiac cycles in the LMCA, the proximal LAD, and the mid-LAD. The pulsatile variation in 11 patients with plaques (5·8 (3·1)%) was much lower than in segments in the normal group ($p < 0·001$) (fig 7).

Discussion

Davidson *et al* reported that IVUS might be useful in demonstrating angiographically "silent" plaques.[11] Davies *et al* used IVUS to show a left main stem stenosis in a patient who had chest pain at rest but no angiographic evidence of stenosis.[16] The case shown in fig 4 resembles the case reported by Davies *et al*. We found atherosclerotic plaques in the LCA at 17% of the angiographically normal sites in 46% of our patients. These results suggest that IVUS can provide evidence of coronary atherosclerosis in patients with symptoms who have normal or inconsistent angiographic findings. None the less, a cause and effect relation cannot be assumed. Such a relation is more likely, however, when there is corroborating functional evidence of ischaemia from stress echocardiography and thallium scintigraphy or evidence of impaired coronary flow reserve. Moreover, IVUS gives information about the plaque characteristics

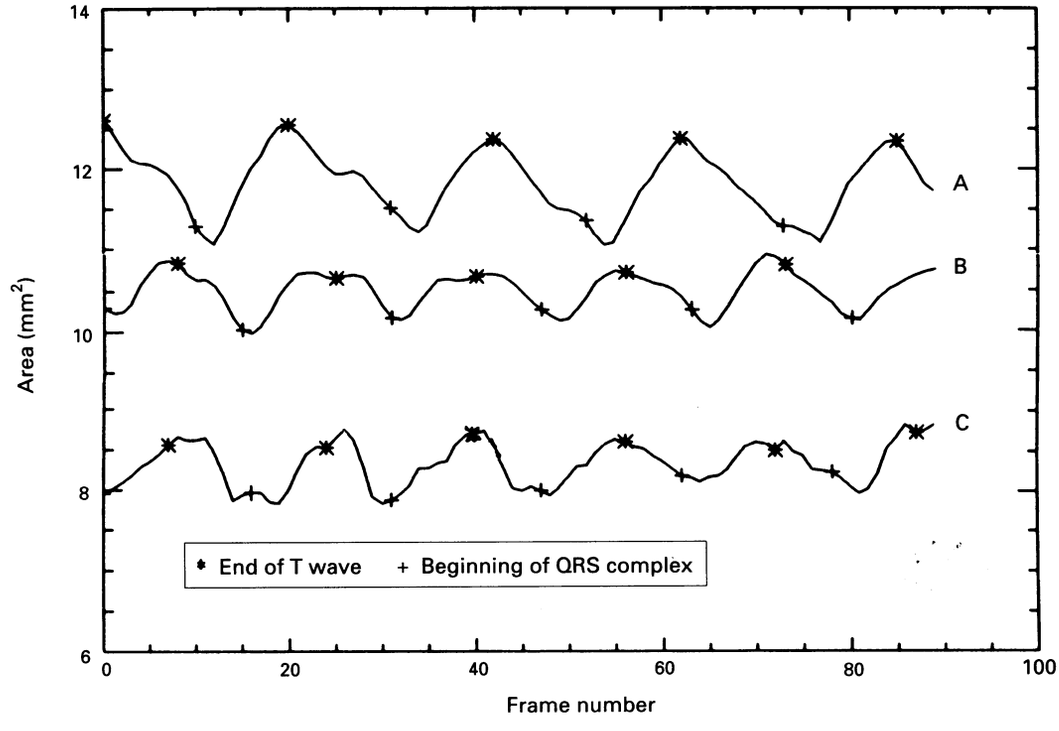

Figure 6 Pulsatile variation in the cross sectional area of the LMCA (A), proximal LAD (B), and of the mid LAD (C) in 90 consecutive frames.

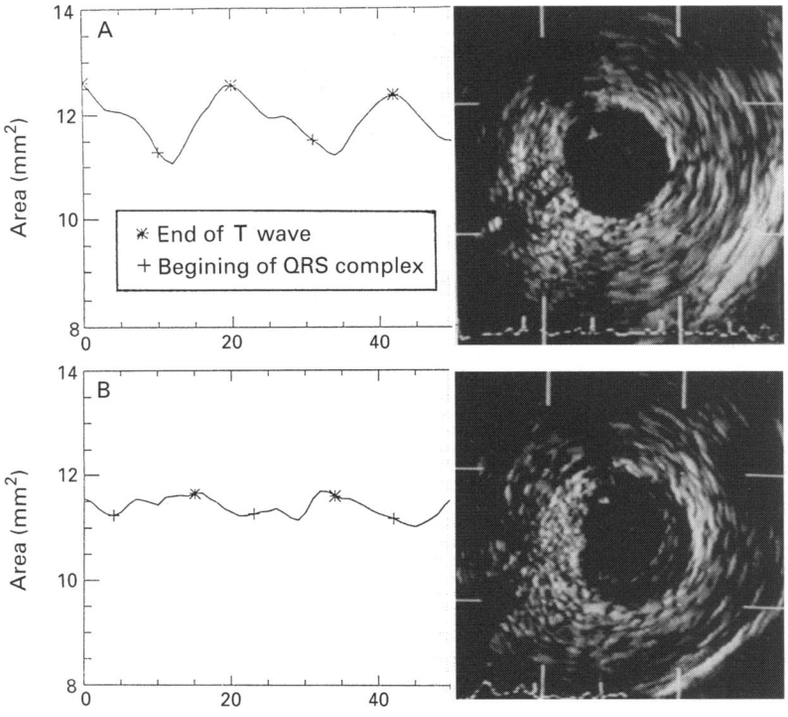

Figure 7 Comparison of the pusatile variation of the cross sectional area of a normal (A) coronary artery and of a coronary artery with an eccentric plaque (B).

(concentric, eccentric, calcified). These findings might be helpful for patient management and predicting prognosis.

Preliminary in vitro studies showed a close correlation between intravascular ultrasonic and anatomical measurements of vessel dimensions,[12–14] but results of in vivo studies were not consistent.[9–11 15] Davidson *et al* reported that the correlation coefficients between ultrasonographic and digital subtraction angiographic measurements were 0·97 for vessel diameter and 0·95 for vessel area.[11] Nissen *et al* and Ge *et al* reported similar results.[10 15] On the other hand, Tobis *et al* reported a correlation coefficient of 0·26 for IVUS and angiographic measurements for vessel area.[9] In the present study, however, there was a close correlation between IVUS and angiographic measurements for lumen diameter and area at normal sites ($r = 0·93$, SEE = 0·43 mm, $p < 0·001$; and $r = 0·89$, SEE = 4·27 mm², $p < 0·001$, respectively). An experimental study in our laboratory showed that incorrect programming of the IVUS device can result in misrepresentation of vessel dimensions.[17] The poor correlation between IVUS and angiographic measurements in vivo might be caused by (*a*) difficulties in using the catheter tip to calibrate for quantitative angiography; (*b*) difficulties in matching the sites measured by IVUS and angiography; (*c*) assessment of coronary dimensions in different phases of the cardiac cycle; and (*d*) errors resulting from incorrect software calibration of the IVUS device.

Table 2 Cross sectional areas of normal LCA during cardiac cycle (mean (SD))

	Maximum (mm²)	*Minimum (mm²)*	*End diastole (mm²)*	*Pulsation (%)*
LMCA	18·33 (8·18)	16·49 (6·77)*	17·33 (7·98)*	10·2 (4·0)
Range	9·74–36·02	8·83–29·95	9·12–30·71	
Proximal LAD	14·01 (5·54)	12·95 (5·08)*	13·56 (5·85)†	8·3 (4·7)
Range	6·91–26·21	6·34–23·61	6·42–26·10	
Mid LAD	10·70 (4·47)	9·78 (4·24)*	9·75 (4·67)*	9·8 (4·0)
Range	4·78–22·74	4·49–21·47	4·53–22·01	

*$p < 0·001$; †0·005. LMCA, left main coronary artery; LCA, left coronary artery.

The dimensions of normal human coronary arteries have been measured in several postmortem studies; some of the measurements were obtained from sections made using pressure perfusion techniques.[18–20] However, postmortem measurements may not accurately reflect coronary dimensions during the cardiac cycle.[20] Data on the normal values of coronary arteries in living subjects are limited and all are based on coronary angiography.[21–23] Area determination by quantitative angiography does not take account of the marked luminal irregularities sometimes found in diseased coronary arteries. We found that 17% of the angiographically normal sites in coronary arteries were not really normal. Moreover, the lumen dimensions varied during the cardiac cycle. We suggest that the dimensions obtained by IVUS are more accurate than those measured by angiography and postmortem studies. We showed that the cross sectional area of the lumen reached a maximum in early diastole. This accords with studies of the circumflex coronary artery in anaesthetised dogs.[24] The change in the cross sectional area of the lumen of normal coronary arteries during the cardiac cycle was 10·2 (4·0)% in the LMCA, 8·3 (4·7)% in the proximal LAD, and 9·8 (4·0)% in the mid LAD. This change in area was much less in segments containing plaques in 11 patients with atherosclerosis. IVUS detected atherosclerosis in almost half of the patients in our study with normal angiograms. The clinical implication of these results remains to be clarified by long-term clinical follow up. Repeat catherisation and IVUS may well provide important pathophysiological and clinical information in patients with evidence of continuing coronary ischaemia.

We also measured the pulsatile variation in cross sectional area during the cardiac cycle. We established that this variation is too large to be ignored when these dimensions are measured. This finding shows that the pulsatile variation in dimensions must be taken into account when measurements derived from the IVUS image are compared with other imaging methods. Moreover, the pulsatile variation of the cross sectional area may offer a new index in evaluating the vascular function.

LIMITATIONS OF THE STUDY

With IVUS, as with transthoracic M mode or cross sectional echocardiography, the cardiac cycle causes the portion of the transducer on the chest wall to move in relation to the heart. We found that although the position of the IVUS catheter was fixed by the "Y" adaptor and guidewire, its position in relation to the vessel wall probably changed during the cardiac cycle. Thus the pulsatile variation of

the vessel lumen may be affected by a shift in the frame caused by cardiac events. Furthermore, long term follow up study will be needed to analyse the clinical significance of the plaques detected by ultrasound. We used a 20 MHz transducer. New studies showed that transducers with higher frequency may improve the resolution[25] and may provide further insights into the atherosclerotic process.

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